169 have been added. No new matter has been added by such amendments. Applicant requests entry of the present amendment.

Objection to the Disclosure

The disclosure is objected to as it is asserted on page 90, line 20, that the passage "a mini-ultracentrifuged 45k rpm at 20°C for four hours" is not adequate description of a centrifugation experiment, as the rotor or the gravitational force must be identified in order to allow one skilled in the art to reproduce the experiment. In reply, applicant traverses the objection and points out that there are standard rotor sizes for mini-ultracentrifuges which would be known to one of skill in the art at the time the application was filed. Thus, to one skilled in the art, "a mini-ultracentrifuged 45k rpm at 20°C for four hours" would constitute an adequate description to carry out the centrifugation step.

Example 2 has been objected to as it is asserted that it does not make any sense, in particular the first paragraph. Applicant has amended the paragraph in question to remove redundancies, such as removing reference to filling a tube with the filtered cesium chloride solution as this was already performed in a previous step, and correcting various typographical errors. Applicant believes the Example would be well understood by the skilled artisan. Should the Examiner believe any further changes are necessary, he is invited to contact applicant's attorney to specify such changes.

It is asserted the primers in the PCR experiment on page 96, line 14, are not described or identified by sequence identification numbers. Applicant asserts that no such identification is required for the following reason.

A nucleotide sequence must be represented by a sequence identification number under 37 C.F.R. §§1.185 *et seq.* only if an unbranched sequence of 10 or more nucleotides is present in the application. As only reference to a primer is indicated on page 96, line 14, and no unbranched sequence of 10 or more nucleotides is described in this particular location of the application, there is no requirement to identify such a primer by a sequence identification number.

The Action requires trademark names used in the application, such as "OptiSeal" on page 92, line 23, and "Dynatech", on page 93, line 24, to be capitalized wherever they appear and be accompanied by the generic terminology. Applicant thanks the Examiner for noting these errors which have now been corrected. Entry of the amendments to the specification correcting these errors is respectfully requested.

The specification is objected to as it is asserted it fails to provide proper antecedent basis for "at least 1 kb in size" in claim 121, "at least 5 kb in size" in claim 122, "at least 10 kb in size" in claim 123, "at least 15 kb in size in claim 124, "at least 20 kb in size" in claim 125, "at least 25 kb in size" in claim 126, "at least 30 kb in size" in claim 127, "at least 40 kb in size" in claim 128, "at least 60 kb in size" in claim 129 and "at least 200 kb in size" in claim 131. As claims 121-131 have been cancelled, this rejection is now moot.

In light of the above discussion, withdrawal of the above-recited objections to the disclosure is respectfully requested.

Claim Objections

Claims 7 and 69; 16 and 76; 21, 82, 156, and 165; 30, 87, 146 and 158; 79, 139, and 140; 135; and 138 are objected to under 37 C.F.R. §1.75(d)(1) as being improper Markush groups. It is asserted that: the members of the Markush group of: (1) claims 7 and 69 are different chemical compounds that do not share a common structural feature required for the stated utility; (2) claims 16 and 76 represent different enzymatic activities and do not share a common utility and a structural feature for the stated utility; (3) claims 21, 82, 156 and 165 are various kinds of organisms that do not share a common structural feature required for the stated utility; (4) claims 30, 87, 146 and 158 are independent methods of mutating nucleic acid sequences and as such each of the methods have different steps and provide different products; (5) claims 79, 139, 140 are various source and geographical locations and do not share a common function or a structural feature required for the function; (6) claim 135 are different chemical entities having no common utility or a structure required for such a utility; and (7) claim 138 do not share a common structural feature required for the stated function. Claim 135 has been amended to recite only polyketide synthases and new claims 167-169 have been added to recite that the operon produces a polyketide, an anti-cancer agent and an immunosuppressant, respectively. As to the remaining objections, applicant asserts that the Markush groups are proper for the following reasons.

"The materials set for the in the Markush group ordinarily must belong to a recognized physical or chemical class or to an art-recognized class. However, when the Markush group occurs in a claim reciting a process..., it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their

function in the claimed relationship, and it is clear from their very nature or from the prior art that all of them possess this property." M.P.E.P. § 2173.05(h).

Claims 7 and 69 relate to fluorogenic substrates. It is clear that the recited substrates have combinations of atoms that allow them to fluoresce. Such substrates may advantageously be utilized in the claimed screening process and are properly included in a Markush group.

Claims 16 and 76 relate to enzyme activity provided by recited enzymes. All of the recited enzymes participate in catalyzing various reactions and are properly included in a Markush group.

Claims 21, 82, 156, and 165 all relate to extremeophiles. Such organisms all include DNA that may be used to prepare the recited libraries and are properly included in a Markush group.

Claims 30, 87, 146, and 158 all relate to various art-known methods of mutating DNA and are properly included in a Markush group.

Claims 79, 139, and 140 are all environmental samples wherein various organisms may be found. Nucleic acid may be obtained from such organisms to construct the recited libraries. Such samples are properly included in a Markush group.

Claim 138 recites various vectors that may be utilized to form the recited libraries. All have the property of being involved in the transfer of DNA into various cells, are considered an art-recognized class of vectors and are properly included in a Markush group.

Claim 48 is objected to because it contains non-elected subject matter. Claim 48 has been amended to remove the non-elected subject matter.

Claims 53, 55 and 57 are objected to under 37 C.F.R. §1.75 as it is asserted they are a substantial duplicate of claim 1. The Manual of Patent Examining Procedure (M.P.E.P.) §706.03(k) states that "when two claims in an application are duplicates, or else are so close in content that they both cover the same thing...it is proper after allowing one claim to object to the other claim under 35 CFR 1.75 as being a substantial duplicate of the allowed claim." (Emphasis added). As claim 1 has not yet been allowed, the rejection is improper and should be removed solely on that basis. Should the Examiner allow claim 1, applicant asserts that the claims are different in scope and the rejection under 35 U.S.C. § 1.75 is improper.

As mentioned in M.P.E.P. § 706.03(k), "court decisions have confirmed applicant's right to restate (i.e., by plural claiming) the invention in a reasonable number of ways. Indeed, a mere difference in scope between claims has been held to be enough." In the present case, the recited libraries are generated from nucleic acid from a mixed population of cells (claim 1), pooled nucleic acid from a plurality of isolates (claim 53), pooling individual gene libraries from nucleic acid from a plurality of isolates (claim 55), or from nucleic acid from an enriched population of organisms (claim 57). By "isolates", it is meant, as recited on page 8, lines 4-6, of the application "that a particular species, genus, family, order, or class of organisms is obtained or derived from a sample having more than one organism or from a mixed population of organisms." By "enriched population", as recited on page 8, lines 12-14, of the application, it is meant "a population of organisms wherein the percentage of organisms belonging to a particular

species, genus, family, order or class of organisms is increased with respect to the population as a whole." Therefore, as the source of the nucleic acid recited in the claims varies (e.g., from a mixed population of cells in claim 1; from pooled nucleic acid from a plurality of isolates in claim 53; from pooling individual gene libraries from nucleic acid from a plurality of isolates in claim 55; or from nucleic acid from an enriched population of organisms in claim 57), each of the claims are of different scope and are therefore proper under 37 C.F.R. § 1.75.

Claims 109, 110 and 116 are objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 63. As claim 63 has not yet been allowed, such a rejection is improper under M.P.E.P. § 706.03(k) as explained above with respect to the rejection of claims 1, 53, 55 and 57 under 35 U.S.C. § 1.75. When claim 63 is allowed, such a rejection is improper for the following reasons. The libraries recited in the claims are obtained from nucleic acid derived from different sources (e.g., a mixed population of cells as in claim 63; pooling individual gene libraries from nucleic acid from a plurality of isolates as in claim 109; from nucleic acid from an enriched population of organisms as in claim 110; and from an environmental source as in claim 116) and are thus of different scope. As each of the claims are of different scope, the objection to the claims is improper.

Claims 12, 119 and 137 are objected to under 37 C.F.R. § 1.75(c) as it is asserted the dependent claims fail to further limit the subject matter of a previous claim.

Claim 1, of which claim 12 depends, recites, among other things, "comparing the bioactivity or biomolecule from b) with the specified bioactivity or biomolecule." The biomolecule could be, for example, nucleic acid, protein, or other biomolecule described in the

specification. Claim 12 further narrows claim 1 by requiring the biomolecule that is compared to be nucleic acid, and specifically requires comparing the variegated nucleic acid sequence of interest to the non-variegated nucleic acid sequence.

Claim 116, of which claim 119 depends, requires, among other things, screening for a desired bioactivity or biomolecule containing a mutation. The biomolecule may be, for example, a nucleic acid as described, for example, on page 8, lines 26, of the application. As the biomolecule may be DNA, and claim 119 requires expression of the mutagenized DNA molecule, claim 119 properly narrows claim 116.

Claim 137 recites that the DNA molecules of claim 116 are inserted into a vector prior to step a). No such vector that includes the recited DNA molecules is recited in claim 116. Therefore, claim 137 further properly narrows claim 116.

Withdrawal of the claim objections discussed in this section of the Response under 37 C.F.R. § 1.75 is respectfully requested.

Rejection under 35 U.S.C. § 101

Claims 63, 109, 110, 116, 119-125, 127, 129, 131, 132, 136-138 and 141-142 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 41-49, 52, 55, 56, 60, 63, 68 and 69 of co-pending application no. 09/375,605. As claims 121-125, 127, 129 and 131 have been cancelled, the rejection as to these claims is now moot. Applicants request the Examiner to hold the rejection as to claim 116, and the claims ultimately dependent thereon (119-120, 132, 136-138 and 141-142), in abeyance until all other rejections have been

officially obviated in this case or in the '605 application. In regard to the rejection relating to the remaining claims, applicants assert the remaining rejected claims do not recite the same invention as the above-referenced claims of application no. 09/375,605 for the following reasons.

A test for double patenting under 35 U.S.C. § 101 is "whether a claim in an application could be literally infringed without literally infringing a corresponding claim in the patent." *Manual of Patent Examining Procedure* § 804, *citing In re Vogel*, 164 U.S.P.Q. 619 (C.C.P.A. 1970).

Claims 63, 109, and 110, recite, among other things, screening of a library prior to variegating a nucleic acid sequence whereas claim 41 requires creating a DNA library prior to introducing at least one mutation followed by screening. Claims 63, 109 and 110 could be literally infringed without infringing claim 41 as the step of "creating a DNA library" is not performed in claims 63, 109, and 110. As claims 63, 109, and 110 do not recite the same invention as the above-indicated claims from co-pending application no. 09/375,605, withdrawal of the rejection of these claims under 35 U.S.C. § 101 is respectfully requested.

Obviousness-Type Double Patenting Rejections

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117 and 119-166 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,939,250 in view of the prior art as exemplified by U.S. Patent No. 5,605,973 to Stemmer et al.

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117 and 119-166 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 5,958,672 in view of prior art as exemplified by U.S. Patent No. 5,316,935 to Arnold et al. and U.S. Patent no. 5,605,793 to Stemmer et al.

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 62-87, 89, 98-108, 111, 117, 126, 128, 130, 133-135, 140 and 143-166 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-70 of U.S. patent application serial no. 09/375,605 in view of the prior art as exemplified by U.S. Patent No. 5,316,935 to Arnold et al. and U.S. Patent No. 5,605,793 to Stemmer et al.

Although applicant believes the above-referenced claims are clearly non-obvious over the cited art, applicant stands ready to submit a terminal disclaimer to obviate the above-referenced obviousness-type double patenting rejections once the claims are deemed to be in condition for allowance. Until that time, applicant requests the Examiner to hold this rejection in abeyance.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117 and 119-166 stand rejected under 35 U.S.C. § 112, second paragraph.

It is asserted that the phrase "bioactivity or biomolecule" in claims 1, 53, 55, 57, 58, 63, 109-111 and 116, and the phrase "mixed population of cells" in claims 1 and 63 render the claims indefinite. For examination purposes, the phrase "bioactivity or biomolecule" was taken

to mean any chemical entity that can be detected. Applicants believe the scope of the rejected claims are definite for the following reasons.

Definiteness of claim language must be analyzed in light of among other things, "the content of the particular application disclosure" and "the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." *Manual of Patent Examining Procedure* § 2173.02 (2001). The specification is replete with examples of bioactivities and biomolecules that fall within the scope of the rejected claims. For example, page 8, lines 24-26, of the application recites a "bioactivity" as, "e.g., an enzymatic activity, secondary messenger activity, binding activity, transcriptional activity and the like." Additionally, examples of biomolecules include, for example, a nucleic acid sequence, a peptide, a polypeptide, a lipid or other small molecule, and the like" as recited on page 8, lines 26-27, of the application. The Background of the application further provides examples of the definitions of the terms "bioactivity" and "biomolecule", and includes in this definition molecules useful in biologics, diagnostics, therapeutics and for industrial applications. One skilled in the art would be familiar with these bioactivities and biomolecules, and other bioactivities and biomolecules encompassed by the claims.

Turning now to the rejection relating to the phrase "mixed population of organisms", such a phrase is not only defined as "more than one organism" on page 3, line 7 and page 7, lines 21-22 of the application, one skilled in the art would readily understand the phrase. In light of the information disclosed in the specification and the claim interpretation that would be given by

one possessing the ordinary level of skill in the pertinent art at the time the invention was made, the rejected claims are considered definite by the skilled artisan.

Claims 1, 53, 55, 57, 58, 63, 109, 110 and 116 are rejected as being incomplete method claims as it is asserted they omit essential steps, such as a step of isolating the DNA of interest before the mutagenesis step and a screening step for bioactivity following the variegating step. Applicant asserts the claims fully comply with 35 U.S.C. § 112, second paragraph, and their scope would thus be clear to a person of ordinary skill in the art for the following reasons.

Definiteness of claim language must be analyzed in light of among other things, "the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." *Manual of Patent Examining Procedure* § 2173.02 (2001). The application explains in detail the methods for obtaining a bioactivity or biomolecule of interest. Such methods are described generally on pages 7-11 of the application, and are more fully described in other locations in the application. One skilled in the art would therefore understand the scope of the rejected claims.

Claim 1 is rejected as being indefinite as it is asserted that a step of screening for a desired bioactivity following the variegation step is needed. As recited above, claim 1 would be considered definite to the skilled artisan and such a rejection is improper. Applicant notes out that final step of claim 1 is directed to "comparing the bioactivity or biomolecule from b) with the specified bioactivity or biomolecule wherein a difference...is indicative of an effect..." Without conceding the correctness of the Exmainer' s position, applicant points out that the

"comparing" step fulfills the "screening" requirement that the Examiner deems to be essential to the claim.

It is asserted that the phrases "oligonucleotide comprising a detectable molecule" in claim 4, "labeled with a fluorescent molecule" in claim 9, "oligonucleotide substantially...and having a detectable molecule" in claims 11 and 77, "oligonucleotide probe comprising a detectable molecule" in claims 58 and 66 and "labeled with a fluorescent molecule" in claim 71 render the claims indefinite. It is asserted in the science of chemistry that a molecule is defined as a single chemical entity and that it is thus not possible to have an oligonucleotide (a molecule) comprising another detectable molecule. The recited claim language would be considered definite to a person of ordinary skill in the art for the following reasons.

The term "comprising" as used in the rejected claims is synonymous with, for example, "containing" or "including". Therefore, one skilled in the art would understand that the recited oligonucleotide in claims 58 and 66 includes a detectable molecule. Additionally, claims 4 and 71 which include recitation of an oligonucleotide that is "labeled with a fluorescent molecule" are not indefinite. One skilled in the art understands that one molecule can be labeled with another molecule, including labeling of an oligonucleotide with a fluorescent or other molecule. Similarly, the oligonucleotide recited in claims 11 and 77 having a detectable molecule would also be readily understood by one skilled in the art to mean the oligonucleotide is labeled, or is otherwise associated with, the recited detectable molecule.

Claims 6 and 68 are rejected as it is asserted that phrase "optical fluorescence" is confusing as it is asserted one of ordinary skill in the art would not know any other kind of

fluorescence and the specification does not teach any other kind. Although applicant believes the phrase in question would be understood by the skilled artisan, claims 6 and 68 have been amended to remove the objectionable term in question in a sincere attempt to advance prosecution.

Claims 7 and 69 are asserted to be indefinite due to the term "or analogue thereof", claims 23, 48 and 105 are asserted to be indefinite due to the terms "bioactive substrate" and claim 24 is asserted to be indefinite due to the term "substrate comprises C12FDG". Although applicant believes the terms recited in claims 7 and 69 to be definite, applicant has amended these claims to remove the objectionable language.

Although applicant believes the term "bioactive substrate" is well known to the skilled artisan, claim 23 has been cancelled and claims 48 and 105 have been amended to remove reference to "bioactive."

Additionally, with respect to the recitation of C12FDG in claim 24, one skilled in the art would be aware that C12FDG is the abbreviation used for the fluorogenic substrate 5-dodecanoyl fluorescein di-beta-D-galactopyranoside, and such is mentioned on page 32, lines 15-16, of the application.

Claim 25 has been rejected as being indefinite as it is asserted the clause "wherein modulation of the interaction of the first protein linked to the DNA binding moiety with the second test protein linked to the transcription activation moiety results in a change" does not make clear the purpose of the first and second test peptides and how the DNA binding moiety

will affect the transcription. Claim 25 has been amended to remove reference to the substrate being labeled with a detectable molecule, as such a label is not required, for example, when practicing claim 25. One skilled in the art would understand the scope of claim 25 for the following reasons.

As explained on page 78 of the application, the yeast "two-hybrid" system traditionally has allowed for identification of polypeptide sequences which bind to predetermined polypeptide sequences wherein the predetermined polypeptide sequence is present in a fusion protein. The approach traditionally identifies protein-protein interactions *in vivo* through reconsitution of a transcriptional activator. Variations of the yeast two-hybrid system have been utilized in the art, including use of a variant of the system to identify interacting protein sequences (i.e., protein sequences which heterodimerize or form higher order heteromultimers) as recited on page 79, lines 14-16, of the application.

In the present case with respect to claim 25, the substrate may be a first test protein linked to a DNA binding moiety and a second test protein linked to a transcriptional activation moiety. The test proteins may be selected such that they will not interact until another component is produced (such as the component being screened for). When the "multimer" is formed, the DNA binding moiety and the transcriptional activation moiety will be in sufficient proximity to each other to interact and bind to a desired nucleic acid sequence to drive transcription of the sequence and, subsequently in one form of the invention, a change in the expression of a detectable protein encoded by the sequence. Such procedures are well known to the skilled artisan and thus claim 25 is definite to such a person.

Claim 27 is rejected as it is asserted it refers to a step (d) in claim 1 and no such step is present in the claim. Applicant thanks the Examiner for noting this typographical error. Claim 27 has been amended to refer to (a), not (d).

Claim 41 is rejected as it is asserted that it refers to step (c). Applicant thanks the Examiner for noting this typographical error. Claim 41 has been amended to refer to "(b)", not "(c)".

Claim 66 has been rejected as indefinite in regard to use of the term "chromogenic or fluorogenic substrate" as it is asserted the term "substrate" is used in the application as enzyme substrate. Applicant believes the Examiner meant to refer to claim 67, as the above-referenced term is not found in claim 66. Use of the term "chromogenic or fluorogenic substrate" would be well understood by one skilled in the art. A substrate as used in the application on page 28, lines 19-28, includes, for example, substrates for the detection of a bioactivity or biomolecule, and lists enzymes as only one example. Additional substrates are discussed, for example, on page 29 wherein it is mentioned that fluorogenic substrates and chromogenic substrates may be utilized. The term "chromogenic or fluorogenic substrate" would be well understood by the skilled artisan.

Claims 79 and 139 are rejected as being indefinite The Action takes the clause to mean, for examination purposes, the environmental sample is obtained from ice, water, permafrost, a close proximity to volcanic vents, soil and plants. Claims 79 and 139 would be understood by one skilled in the art for the following reasons.

Claim 79 depends from claim 78, which recites that the library contains DNA obtained from an environmental sample. Similarly, claim 116, from which claim 139 depends, recites a DNA library comprised of DNA molecules obtained directly from an environmental source. Claim 79 specifies the nature of the environmental sample and claim 139 has been amended from specifying the nature of the environmental sample to specifying the nature of the environmental source for proper antecedent basis. As the rejected claims recite the nature of the environmental sample or source from which the recited DNA has been obtained, they would be considered definite to the skilled artisan and use of the term "obtained from" as suggested in the Action would be redundant. Additionally, one skilled in the art would be familiar with the term "materials of volcanic origin" and materials that are in close proximity to volcanic vents represent one such example of materials of volcanic origin. One skilled in the art would also be familiar with other materials of volcanic origin and thus the recited term would be definite to the skilled artisan.

Claim 119 is rejected as indefinite as it is asserted that it refers to a step (b) in claim 116 and such a step is not present in the claim. Applicant thanks the Examiner for noting this typographical error and has amended claim 119 to remove reference to such a step.

Claim 137 is rejected as indefinite as it is asserted that the claim refers to step (a) of claim 116, but claim 116 does not have a step (a). Applicant thanks the Examiner for noting this typographical error and has amended claim 137 to remove reference to such a step.

A rejection relating to use of the term "fosmids" in a claim as being indefinite was made in the Action, although the specific claim number was not mentioned. Applicant assumes the

Action is referring to claim 138 which includes the term "fosmid". The term "fosmid" is well understood by the skilled artisan as shown by, for example, the text on page 22, lines 13-20, of the application and the abstract of an article by Kim, et al. *Nucleic Acids Res.* 20(5):1083-1085 (1992) included herewith.

Claims 144, 148 and 166 have been rejected as indefinite as it is asserted the term "improved activity" is not defined by the specification and one of ordinary skill in the art would not know in which way the activity was improved. Applicant asserts the term is definite and one of ordinary skill in the art would be well aware of the way the activity was improved for the following reasons.

One skilled in the art would know that "improved activity" would be defined depending on the nature of the molecule of interest. The improved activity may refer to, for example, (1) an enzyme, and would mean that enzymatic activity is improved, including an increase in the rate of reaction catalyzed by the enzyme or some other parameter; (2) a ligand, such that binding activity is improved (e.g., stronger binding affinity between a ligand and its binding site); (3) a transcriptional activator, such that the transcriptional activity is improved by, for example, allowing for an increased amount of transcripts to be formed; or (4) other molecules having specified functions as known to the skilled artisan. One skilled in the art would be familiar with the nature of such improved activities, notwithstanding that such activities are delineated on page 8, lines 24-26 of the application, and would be familiar with other activities that may be improved.

In light of the foregoing statements in this section, withdrawal of the rejection of claims 1-30, 32, 41-51, 53, 55, 57, 58, 63-87, 89, 98-111, 116, 117 and 119-166 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. § 102 (e)

Claims 1-6, 8-24, 27, 28, 30, 41-48, 50, 51, 53, 55, 57, 58, 63-68, 70-87, 98-105, 107-111, 116, 117, 119-143 and 157-166 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,824,485 to Thompson et al.

The claimed invention is directed to a method for obtaining a bioactivity or a biomolecule of interest, comprising: a) screening a library of clones generated from nucleic acids obtained directly from a mixed population of cells, for a specified bioactivity or biomolecule; b) mutating a nucleic acid sequence contained in a clone from the library having the specified bioactivity or biomolecule; and c) comparing the bioactivity or biomolecule from b) with the specified bioactivity or biomolecule wherein a difference in the bioactivity or biomolecule is indicative of an effect of sequence mutation, thereby providing the bioactivity or biomolecule of interest.

Three types of libraries are discussed in Thompson et al.: (1) combinatorial natural pathway expression libraries; (2) combinatorial chimeric pathway expression libraries; and (3) biased combinatorial gene expression libraries. See claims 1-3 in col. 97 of Thompson. The libraries are prepared from genetic material that has been pre-selected for a specific property or from genetic material that is a derivation of what exists in a donor organism (see Thompson claims 1-3). Thompson states "the genetic material used to prepare the libraries can be obtained

directly from an environmental sample" on lines 51-53 of col. 12.[1] However, this phrase is in the context of describing specifically *donor organisms* (see title of § 5.1.1 in col. 12) and not in the context of creating the library itself. Thompson discloses taking the genetic material "obtained directly from an environmental sample" and pre-selecting it prior to making the library. See, for example, col. 41, lines 25-50. Thompson also describes in col. 39, beginning at line 49, methods "for extracting, selecting and preparing high quality nucleic acids from culture of donor organisms." Thompson describes concentration of microbial samples, or amplification of DNA prior to creation of the library (see col. 17, lines 8-62). In contrast, the claimed invention requires "creating a DNA library comprised of DNA molecules obtained directly from an environmental source" (see step (a) of claim 41). For this reason, Thompson does not anticipate the claimed invention.

Furthermore, there is no teaching or suggestion of "introducing at least one mutation into a nucleic acid sequence" as recited in the pending claims. Combinatorial chimeric_pathway expression libraries are described in column 6, lines 28-35, of Thompson et al. as including randomly concatenated genetic material derived from one or more species of donor organisms in which genes present in the genetic material are operably associated with regulatory elements. The purpose of the chimeric pathway expression libraries is to form a discrete gene set from genes from donor organisms that produce functional gene products of the donor, wherein the gene products can interact to form novel chimeric metabolic pathways to produce novel classes

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[1] Applicants do not concede that the quotation from Thompson is supported in either of the priority documents (*i.e.*, U.S. Serial No. 427,244, filed April 25, 1995 and U.S. Serial No. 427,348, filed April 25, 1995). Accordingly, applicants do not concede that Thompson is entitled to the priority date of April 25, 1995 for this disclosure. Thompson (the '485 patent) is a continuation-in-part of the two aforementioned applications.

of compounds. This is further supported in column 9, lines 1-6, of Thompson et al. wherein it is mentioned, regarding the combinatorial gene expression libraries described generally in the patent, that:

> These libraries comprise random assortments of gene products of multiple species which are in some cases allowed to interact with each other in the expression host, and result in some cases in the formation of novel biochemical pathways and/or the production of novel classes of compounds.

However, there is no teaching or suggestion of taking those libraries and "introducing at least one mutation into a DNA molecule from said library to create a mutagenized DNA molecule" as recited in step (b) of claim 41. As described above, Thompson et al. teach libraries that include combinations of genes from one or more species of donor organisms wherein the genes are not modified, are produced in the host organism and wherein the gene products may interact to form either a chimeric biochemical pathway or a naturally-occurring biochemical pathway to obtain novel compounds.

Withdrawal of the rejection of claims 1-6, 8-24, 27, 28, 30, 41-48, 50, 51, 53, 55, 57, 58, 63-68, 70-87, 98-105, 107-111, 116, 117, 119-143 and 157-166 under 35 U.S.C. § 102(e) is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 5-7, 9, 13, 24, 26, 29, 32, 48, 49, 58, 66-71, 85, 86, 89, 106, and 144-156 stand rejected under 35 U.S.C. § 103 as being unpatentable over Thompson et al. in view of the state of the art as exemplified by U.S. Patent No. 5,811,238 to Stemmer et al. and U.S. Patent No. 5,316,935 to Arnold et al. Thompson et al. is relied on for teaching, among other things, that

recited in the 102(e) rejection above. Arnold et al. is relied on for teaching a method of obtaining mutants of subtilisin with desired characteristics which includes random mutagenesis of the gene encoding the enzyme by various methods, incorporating the mutated population of genes into expression vectors, transforming suitable cells and screening for a colony expressing a subtilisin mutant with desired characteristics. Stemmer et al. is relied on for teaching a method of identifying proteins having desired and improved activity using a nucleic acid shuffling mutation method, constructing a library and screening the library for desired activity.

It is asserted in the Office Action that Thompson et al. provides the motivation for one of ordinary skill in the art to isolate a biological molecule of interest from an environmental sample, generate a library of chimeric genes, and screen for a desired biological product. It is further asserted in the Office Action that Stemmer et al. provides one of ordinary skill in the art with motivation to develop a method of identifying a protein with modified activity by generating a heterologous population of DNA from a gene by mutagenesis. It is concluded in the Office Action that one of ordinary skill in the art would have obtained an environmental sample, constructed a gene or cDNA library, normalize the library by well known methods, screen for desired bioactivity, isolate the DNA encoding the desired bioactivity as taught by Thompson et al., subject the gene or DNA to one of several random mutation methods taught by Stemmer et al. and Thompson et al., construct an expression library comprising the heterologous DNA population and screen for desired improved activity by well known methods in the art.

Applicants maintain that there is no motivation to combine together the cited references. Furthermore, contrary to the assertions in the Office Action, none of the cited references either

alone or combined teach, suggest or motivate one skilled in the art to arrive at the claimed invention for the following reasons.

The remarks distinguishing the claims of the present application from the teachings of Thompson et al. discussed with respect to the rejection under 35 U.S.C. § 102(e) apply equally here. Applicant maintains that there is no motivation to combine the references and even if the references were combined, taken together, they do not teach or suggest the claimed invention. The asserted rejection lacks the specificity needed in finding a motivation to combine references.

"[P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed..." (*underlining added*, *In re Kotzab*, 217 F.3d 1365, 1375 (Fed. Cir. 2000)). The Examiner has pointed out that one of skill would be motivated by Thompson to do exactly what is taught by Thompson, i.e., to isolate a gene of interest from an environmental sample and generate a library of chimeric genes, and screen for desired product. There is no indication of the motivation in Thompson to look to either Stemmer or Arnold for additional steps to the method disclosed by Thompson. Similarly, it is asserted that Stemmer provides motivation to one of ordinary skill in the art to do only what is actually disclosed by Stemmer. The method of identifying a protein referred to here is simply the method which is described in Stemmer itself, not motivation to go outside of the reference and combine its teachings with something else. There is no indication by the Examiner of any motivation to one of ordinary skill in the art in one reference cited under 35 U.S.C. § 103 to go to one of the other references also cited, or to improve upon or alter the method in a single reference in any way. It seems that the Examiner

then concludes, based apparently on nothing more than hindsight, that one of skill in the art would have combined Thompson and Stemmer. Thus, the applicant maintains that one of skill in the art would not have been motivated to combine Thompson with Stemmer or Arnold. "Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc.* 159 F.3d 534, 546 (Fed. Cir. 1998).

Even if one were to combine the cited references (absent the required motivation), the combination would not make the claimed invention obvious to one of ordinary skill in the art. The remarks above which distinguish the claimed invention from the Thompson disclosure apply equally here. Furthermore, Stemmer merely discloses reassembly of genes from their random DNA fragments (see Abstract). There is no teaching or suggestion of step (a) of claim 1 directed to screening a library of clones generated from nucleic acids obtained directly from a mixed population of cells. Thus, the combination of Thompson and Stemmer does not teach or suggest the claimed invention. Similarly, the combination of Arnold et al. to the pairing of Thompson and Stemmer does not teach the claimed invention. The Arnold patent disclosure does not remedy the shortcomings of the combination of Thompson and Stemmer, in that Arnold does not teach or suggest mutating a nucleic acid sequence contained in a clone from a library of clones generated from nucleic acids obtained directly from a mixed population of cells.

In conclusion, applicant maintains that the claimed invention is not rendered obvious by the combination of Thompson, Stemmer and Arnold. In addition, applicant maintains that there is no motivation to combine these three references and that, therefore, this rejection is improper

under the law. In view of these remarks, applicant respectfully requests the Examiner to reconsider and withdraw these grounds of rejection and allow the pending claims to pass to issue.

In view of the foregoing, it is believed that all objections and rejections of records have been overcome, and that the claims are in condition for allowance. Action towards that end is respectfully requested. The Examiner is invited to contact the undersigned attorney by telephone regarding any issues that may be handled in that fashion.

Respectfully submitted,

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